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Section C

Antibiotic Use in Industrial Food Animal Production
Antibiotics: A Landmark Medical Advance

Uses of Antibiotics and Resistance

- Antibiotic uses
  - Clinical medicine
  - Animal agriculture
    - Terrestrial
    - Aquaculture
  - Other uses
    - Crop production
    - Ethanol production

- All uses contribute to resistance development
  - Some contribute more

- The extent of the problem of resistance that can be blamed on antibiotic use in IFAP is unclear
Antimicrobials Registered as Feed Additives in the US*

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Species</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arsenicals</td>
<td>Arsenilic acid</td>
<td>Poultry</td>
</tr>
<tr>
<td></td>
<td>Roxarsone, cabarsone</td>
<td>Poultry</td>
</tr>
<tr>
<td>Polypeptides</td>
<td>Bacitracin</td>
<td>Cattle, pigs, poultry</td>
</tr>
<tr>
<td>Glycolipids</td>
<td>Bambermycin</td>
<td>Pigs, poultry</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>Tetracycline</td>
<td>Pigs</td>
</tr>
<tr>
<td></td>
<td>Chlortetracycline</td>
<td>Cattle, pigs, poultry</td>
</tr>
<tr>
<td></td>
<td>Oxytetracycline</td>
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<td>Elfamycine</td>
<td>Efrotomycin</td>
<td>Pigs</td>
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<td>Macrolides</td>
<td>Erythromycin</td>
<td>Cattle</td>
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<tr>
<td></td>
<td>Oleandomycin</td>
<td>Chicken, turkey</td>
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<tr>
<td></td>
<td>Tylosin</td>
<td>Cattle, pigs, chicken</td>
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<tr>
<td></td>
<td>Tiamulin</td>
<td>Pigs</td>
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<td>Lincosamides</td>
<td>Lincomycin</td>
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<td>Ionophores</td>
<td>Monensin</td>
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<td>Lasalocid</td>
<td>Cattle</td>
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<td>Penicillins</td>
<td>Penicillin</td>
<td>Poultry</td>
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<td>Quinoxalines</td>
<td>Carbadox</td>
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<td>Streptogramins</td>
<td>Virginiamycin</td>
<td>Swine</td>
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<td>Sulfonamides</td>
<td>Sulfamethazine</td>
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</tr>
<tr>
<td></td>
<td>Sulfathiazole</td>
<td>Pigs</td>
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</tbody>
</table>

*Many of these drugs/drug classes are the same as those used in human clinical medicine*
### Usage Estimates (Millions of Pounds per Year)

<table>
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<tbody>
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<td>Human use</td>
<td>32.2</td>
<td>4.5</td>
<td>Not estimated</td>
<td>7.3</td>
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<tr>
<td>Animal (non-therapeutic)</td>
<td>3.1</td>
<td>27.6</td>
<td>27.8</td>
<td>28.8</td>
</tr>
<tr>
<td>Animal (therapeutic)</td>
<td>14.7</td>
<td>2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Data availability
- Estimation methods and conflicting interests
- Divisive terminology
Antimicrobial Use

- Multiple purposes (FDA)
- Treatment
- Control
- Prevention
- Production
  - Growth promotion
  - Feed conversion
Antimicrobial Use

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Eighty percent of antimicrobials in the US are sold for use in food animal production
Antimicrobial Misuse

- Prevention and growth promotion
  - Lower dose
  - Longer duration
  - Feed and water
  - Limited veterinary oversight

Antimicrobial Sales, by Dosage Form, 2009

- Feed: 74%
- Water: 16%
- Other: 10%
- Feed: 74%
Antibiotic Resistance
Origins and Perpetuation of Resistance

- Primary mechanisms of development and dissemination of resistance
  - Natural selection
  - Sharing of resistance genes
  - Mutagenesis
  - Reservoir of resistance

- Recent findings
  - Community dynamics
Resistance Selection

Antibiotic

R.I.P.
Horizontal Gene Transfer

- Bacterial transformation
- Bacterial transduction through phage virus infection
- Bacterial conjugation

Mutagenesis and Resistance

- Bactericidal antibiotics
  - E.g., β-lactams, quinolones, and aminoglycosides

- Application to aerobic bacteria at levels below those that induce selection pressure can make bacteria produce reactive oxygen species (ROS)
  - Hydroxyl radicals

- ROS can be DNA-reactive and produce point mutations

- Accumulation of mutations in bacteria have been shown to induce the development of mutant strains that demonstrate resistance to multiple drugs

Source: Kohanski et al. (2010). *Molecular Cell.*
Reservoir of Resistance

- The “resistome”

- Bacteria that are not pathogenic can harbor genes that confer resistance when shared horizontally with other bacteria

Community Dynamics

- Bacterial altruism

- Bacteria that have mutation allowing drug resistance can share chemical signals with drug-susceptible bacteria

- Formally susceptible bacteria can become resistant

Source: Lee et al. (2010). *Nature.*
Dose Imprecision

- Most antibiotics in IFAP are administered through feed or water

- Numerous factors influence precision in dose delivery
  - Feed quality control
  - Behavior of animal production facility workers
  - Animal/herd dynamics
  - Drug absorption, pharmacokinetics

- It is unlikely that antibiotics can be delivered at predictable or intended doses through feed
Dose Imprecision May Increase Resistance Development Rate

- Over-administration can lead to drug residues in food animal products and clinical toxicity in animals

- Under-administration can lead to genetic mutations that allow resistance to emerge

- Intermittent dosing in which variability can lead to over- and/or under-administration that can then lead to antimicrobial selection pressure and/or disease treatment failure

Exposure, Risk, and Relevant Policy
Pathways of Exposure to Resistant Bacteria

Fig. 3. Spread of antimicrobial-resistant pathogens (X) from agriculture to the community and hospital. Pathogens from CAFOs (pig-farm house) spread through food products, manure lagoons, air, wildlife (birds), animal transport trucks, and deposit of manure on cropland. (Courtesy of Salvador Saenz, El Paso, TX. Copyright ©2008, Salvador Saenz.)

Consequences of Resistant Infections

- Health and economic burden
  - Resistant infections respond poorly to one or more antibiotics and increase mortality risk
    - Estimated 19,000 deaths from HAI in 2001 (IOM, 2008)
      - Extent of burden from animal production not estimated
  - Hospital stays are longer and more costly for resistant infections
    - E.g., MRSA vs. MSSA
      - Hospital stay increased by 14 days (Kim, 2001)
      - Average cost of a hospital stay: $45,920 vs. $9,699 (McHugh and Riley, 2004)
  - Multiple estimates of societal cost of resistant infections
    - IOM (1998) estimated domestic cost to be as high as $30 billion per year
The Danish “Experiment”

- Denmark passed legislation to restrict use of non-therapeutic antimicrobials in swine production
  - Elimination of GPA use in finishing pigs in 1998, and in weaners in 2000

- Results of the ban have since been evaluated with regard to changes in antimicrobial use, animal production indices, and animal health
Results of the Danish GPA Ban

- Indicators of animal health have revealed a beneficial effect (weight gain, mortality)

- Total antibiotic consumption has declined by more than 50 percent

- Reductions in resistance in animal pathogens, indicator bacteria, and zoonotic microorganisms

- Precedent setting: “The United States has an effective model in Denmark to draw upon when it comes to protecting public health.” (NAS, 2010)
Relevant Domestic Policy

  - FDA collects and releases aggregated sales data for antibiotics in food animal production

- Preservation of Antibiotics for Medical Treatment Act (PAMTA)—introduced in current session
  - Limits the use of “medically important” antibiotics in food animal production
Strategies to Address Antimicrobial Resistance Act (STAAR)—introduced in current session

- Data collection and dissemination regarding antibiotics use in humans and animals
- Funding for interagency task force, “real-time” monitoring
Conclusions

- Antibiotics are a critical tool in clinical medicine
- The same antibiotics are used in animal agriculture for non-therapeutic purposes
- Antibiotic use in animal agriculture promotes the emergence and propagation of resistant bacteria
- Many environmental pathways exist for the spread of resistant bacteria from animal production sites to people
- Domestic policies have been proposed to address the use of antibiotics in IFAP